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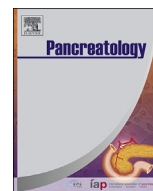
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Pain in pancreatic ductal adenocarcinoma: A multidisciplinary, International guideline for optimized management

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ABSTRACT

Abdominal pain is an important symptom in most patients with pancreatic ductal adenocarcinoma (PDAC). Adequate control of pain is often unsatisfactory due to limited treatment options and significant variation in local practice, emphasizing the need for a multidisciplinary approach. This review contends that improvement in the management of PDAC pain will result from a synthesis of best practice and evidence around the world in a multidisciplinary way. To improve clinical utility and evaluation, the evidence was rated according to the GRADE guidelines by a group of international experts. An algorithm is presented, which brings together all currently available treatment options. Pain is best treated early on with analgesics with most patients requiring opioids, but neurolytic procedures are often required later in the disease course. Celiac plexus neurolysis offers medium term relief in a substantial number of patients, but other procedures such as splanchicectomy are also available. Palliative chemotherapy also provides pain relief as a collateral benefit. It is stressed that the assessment of pain must take into account the broader context of other physical and psychological symptoms. Adjunctive treatments for pain, depression and anxiety as well as radiotherapy, endoscopic therapy and neuromodulation may be required in selected patients. There are few comparative studies to help define which combination and order of these treatment options should be applied. New pain therapies are emerging and could for example target neural transmitters. However, until better methods are available, management of pain should be individualized in a multidisciplinary setting to ensure optimal care.

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Introduction and methods

Pancreatic ductal adenocarcinoma (PDAC) presents in different ways and often at an advanced stage. Abdominal pain is an important presenting symptom in about 60% of patients [1] and

becomes a feature in almost all patients at some stage during the course of the disease. It is a common disabling symptom with several causes, and often difficult to treat, requiring multidisciplinary management for effective control. Pain is also a major predictor of outcome and survival. A striking ubiquitous pathological feature of PDAC is perineural invasion, which might explain its propensity to cause pain.

Recently published guidelines reveal a lack of standardized assessment and management of pain associated with PDAC. Most recommendations for its management are offered within selected specialties, reflecting significant variation in practice and thus emphasizing the need for a multidisciplinary approach. The variation in recommendations may simply reflect customary practice, but also the paucity of evidence on which to base the recommendations.

This review contends that improvement in the management of PDAC pain will result from a synthesis of best practices and evidences from around the world, to integrate the many treatment options, including pharmaceuticals, endoscopic and endosonographic interventions, surgery, neurolysis, neuromodulation, radiotherapy, psychotherapy, nursing and supportive care. Accordingly, the authors were selected to include a wide range of specialists with clinical and research experience in cancer pain management within relevant specialties. The authors were assigned to make recommendations on PDAC pain related issues and giving best available evidence. To improve clinical utility, most recommendations were framed for routine clinical practice. To score the strength of the evidence a modified GRADE method was used (<http://www.uptodate.com/home/grading-tutorial>). Finally, the level of agreement for the stated recommendation was determined by the authors independently voting on-line. Further details relating to methodology and a fuller discussion are available (supplementary material on-line).

Pathogenesis of pain in PDAC

The pathogenesis of pain in PDAC is multifactorial and encompasses neuropathic, visceral and somatic mechanisms. Quality assessment: moderate; Recommendation: moderate; Agreement: strong

The majority of patients with PDAC experience a chronic pain syndrome that is multifactorial in origin [2]. It entails neuropathic mechanisms due to neural infiltration by cancer cells. However, the pathogenesis of pain in PDAC is additionally complex in most cases with evidence of cross talks between pancreatic nerves, vascular system, pancreatic stellate cells and cancer cells. This is reflected in management that should target several mechanisms. In addition, pain can be due to invasion of other visceral and somatic structures. For details and references, see supplementary material.

Pain assessment in PDAC

Pain should be assessed in the context of many other physical and psychological symptoms, with an emphasis on severity, quality, distress and functional consequences. Although there has been focus on pain intensity, pain interference with quality of life should also be addressed. Quality assessment: moderate; Recommendation: strong; Agreement: strong

Pain should be assessed in the context of other multiple physical and psychological symptoms, with an emphasis on severity, quality, distress and functional consequences from a patient's perspective [3]. As pain in PDAC shares mechanisms with those in chronic pancreatitis, assessment tools used in this disease may be adopted to patients with pancreas cancer [4]. Numerical scales, such as the visual analogue scale, are commonly applied to assess the intensity

of pain, but should be combined with a standardized registration of the temporal pain pattern [5]. Patients with PDAC have a very high prevalence of depressed mood, which is higher than other cancers with similar prognoses [6] and in many cases disturbed sleep and fatigue should also be recorded [7]. Pain assessment should also be supplemented with measurement of quality of life (QoL) using instruments such as the Short-Form Health Survey 36 (SF-36) and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [8,9].

Secondary reasons for pain

Pain due to complications associated with treatment and side effects of medication is frequent and should always be considered as additional reason for pain, especially because treatment is often effective. Quality assessment: low; Recommendation: moderate; Agreement: strong

Adverse effects and complications due to surgery, endoscopic, pharmacological and oncological treatments are important causes of morbidity in many patients and should be considered as additional sources of pain (Table 1). As management is often effective, these causes of pain should not be overlooked. Pain can be due to chemotherapy and irradiation, and related to neuropathy and enteritis [10]. Anastomotic and peptic ulcers are common and there should be a low threshold for endoscopic diagnosis. Although strong opioids are often used to relieve pain, they have the potential to produce substantial side effects, including constipation, abdominal pain and opioid induced hyperalgesia that can mimic pain due to PDAC (see section on analgesics). Complications of surgical and endoscopic treatments can also be the cause of pain. These include anastomotic leaks, intra-abdominal collections, acute pancreatitis, perforation and adhesions [11]. Obstruction of the bile duct is almost universal in PDAC of the head of pancreas, while obstruction of the duodenum occurs in up to a quarter of these patients. In patients with unresectable, metastatic and recurrent PDAC, biliary and gastric outlet obstructions are best managed with self-expanding metal stents without the need for surgical bypass, because they have been demonstrated to be safe and effective [12]. Abdominal discomfort can be due to maldigestion following pancreatic resection from a possible combination of exocrine pancreatic insufficiency, bile acid malabsorption and bacterial overgrowth [4,12]. Advanced PDAC may cause pain due to direct invasion into adjacent organs but also from metastases, most commonly to bone, liver and lung [13].

Pain management algorithm

Pain management in PDAC should be individualized, multidisciplinary and follow an algorithm. Quality assessment: moderate; Recommendation: strong; Agreement: strong

Pain management in PDAC should be individualized, but it will also depend on local expertise and skills. In many clinical settings, the treatment of pain follows traditional approaches and several treatment modalities are often overlooked. There is an overall consensus by pain specialists that optimal management of cancer pain should be multidisciplinary [13]. This is illustrated in Fig. 1, where most treatment options are included. The different treatments are often started in parallel, although the sequence of treatments will often depend on stage of PDAC and availability of treatment modalities and expertise. Hence, the algorithm in Fig. 1 shall not be regarded as definitive but as guidance. With a multidisciplinary approach, it is imperative that patients have rapid access to a lead health care professional to coordinate disciplines and taking overall responsibility. Ideally,

Table 1
Secondary reasons for pain in patients with PDAC.

	Suggested investigation	Treatment
Anastomotic and peptic ulcers	Gastroscopy	Proton pump inhibitors <i>H. Pylori</i> eradication
Side-effects to opioids	Clinical judgement	Tapering of medication
Side effects to chemotherapy and irradiation	Clinical evaluation	Co-administration of laxatives in patients on opioid therapy
Somatic pain with irradiation to the abdomen	Objective assessment of the back etc.	Local treatment and drugs against neuropathy
Surgical end endoscopic complications: Anastomosis leaks or strictures, intraabdominal adhesions, pancreatitis	Imaging	Targeted against the somatic pain Conservative treatment, endotherapy or surgery
Duodenal and biliary obstruction	Magnetic resonance imaging	Stent placement
Exocrine pancreatic insufficiency	Pancreatic function testing	Enzyme replacement therapy
Bacterial overgrowth	Breath testing	Antibiotics
Bile acid malabsorption	Se-HCAT scan	Cholestyramine
Delayed gastric emptying	Gastroscopy, scintigraphy	Pro-kinetics
Metastasis and tumor growth to neighbour organs	Imaging	Dependent on localization

Se-HCAT: selenium homocholic acid taurine.

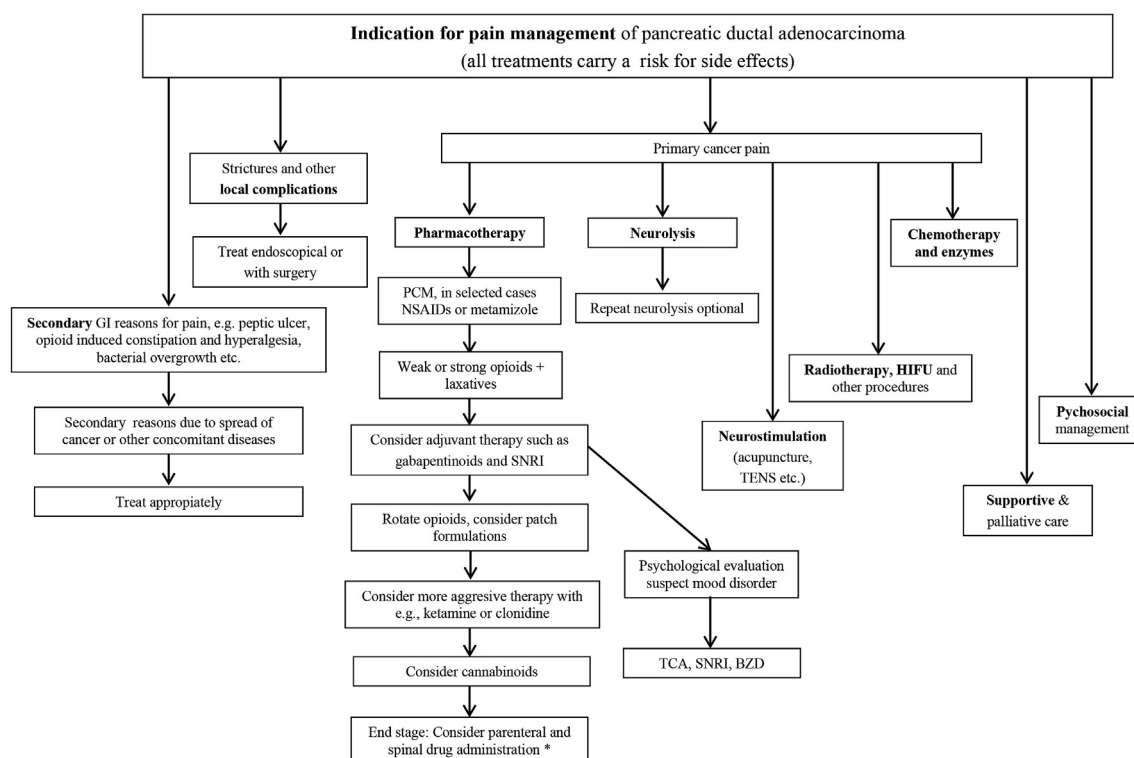


Fig. 1. Simplified algorithm showing the treatment possibilities for optimal management of pain in patients with pancreatic ductal adenocarcinoma. In most cases, the algorithm cannot be strictly followed and combination therapies are necessary. The recommendation is to consider whether pain intensity and effect on quality of life is sufficiently severe to justify treatment, given the potential side effects. In case there is indication for pain management the following is suggested: 1) First it shall be considered whether there can be secondary reasons for pain as this often needs specific treatments. 2) The next step is to evaluate whether local factors such as strictures on the main pancreatic duct need endoscopic or surgical treatment. 3) Primary pain due to tumor infiltration of the nerves and local pressure is treated with a) chemotherapy according to performance status and pancreatic enzymes as well as b) analgesics, see specific section for detail. In case this is insufficient or there are too many side effects, c) neurolysis is considered. The neurolytic treatment depends on local expertise, and timing is important, see specific section. In many patients d) adjuvant therapy with antidepressants and anxiolytics that also have analgesic properties are used, and complementary therapy such as with acupuncture may be used. In some cases, especially when other procedures have failed, treatment with e) radiotherapy or HIFU can also be used. Finally, 4) supportive care and 5) psychosocial interventions are mandatory in the multidisciplinary approach to pain management. * In terminal disease spinal application of opioids, anesthetics and adjuvant analgesics may be used for palliation. GI: gastrointestinal, PCM: paracetamol, NSAID: non-steroidal anti-inflammatory drugs, SNRI: serotonin–norepinephrine reuptake inhibitors, TCA: tricyclic antidepressants, BZD: benzodiazepines, TENS: transcutaneous electrical nerve stimulation, HIFU: high intensity focused ultrasound.

this would be an expert pancreatologist/surgeon/oncologist who should work with a pain or palliative care specialist. Because the progress of PDAC and pain is unpredictable, it is important that patients are well monitored and treatment adjusted.

Non-invasive management of PDAC

Pancreatic enzyme replacement therapy

Pancreatic enzyme replacement therapy may diminish pancreas secretion and normalize gut function, and as such alleviate abdominal

pain. *Quality assessment: moderate; Recommendation: weak; Agreement: weak*

Pancreatic enzyme replacement therapy is used for the management of exocrine pancreatic insufficiency in patients with PDAC, but it may also exert an analgesic effect. The proposed pain relieving mechanism of action is the ability of pancreatic enzymes to degrade cholecystokinin (CCK) releasing factor in the duodenum, whereby CCK-levels are suppressed [14]. In addition to the effects mediated through CCK pathways, normalization of digestion following enzyme replacement therapy may also improve abdominal symptoms. However, their effect on pain in PDAC is not proven.

Chemotherapy

Chemotherapy can reduce pain likely by decreasing tumor load. Quality assessment: moderate; Recommendation: strong; Agreement: conditional

Chemotherapy in unresectable patients may decrease pain by reducing tumor growth, local neural invasion and inflammation. In a meta-analysis in patients with metastatic PDAC, pain relief following chemotherapy was consistently seen for most included studies evaluating pain [15]. Previous studies have shown that gemcitabine compared with 5FU resulted in increased survival and reduced pain [16]. Gemcitabine-based combinations showed no consistent benefit for pain compared with single-agent gemcitabine [17]. The newer regimens FOLFIRINOX (oxaliplatin, irinotecan,

fluorouracil and leucovorin) and gemcitabine/nab-paclitaxel have shown improved survival compared to gemcitabine, and are at present considered standard treatment for patients with good performance status [17,18], although time until deterioration of pain is longer for FOLFIRINOX than with gemcitabine [15].

Analgesics

Currently the guidelines for analgesic therapy in PDAC follows the principles of the “analgesic ladder” provided by the World Health Organization. However, experimental treatment and other analgesics may be beneficial in the individual patient. In end stage disease, more aggressive treatment modalities are often needed. Quality assessment: moderate; Recommendation: strong; Agreement: strong

The “analgesic ladder” is a stepwise escalation of drugs with increasing analgesic potency until pain relief is obtained [19] (Fig. 1, for details see supplementary material). Analgesics should preferably be administered by the oral route (Table 2) at regular intervals. Breakthrough pain is treated with e.g., fast-acting on-demand opioids such as fentanyl. To facilitate the clinical use, the authors' personal recommendations are also shown (Table 2). The most important drug classes are briefly described below:

Non-opioid analgesics are used as the first step in pain management. Paracetamol may be sufficient for patients in whom the pain intensity is mild to moderate. Non-steroidal anti-inflammatory drugs (NSAIDs) are normally avoided, but may be used with a

Table 2
Recommended oral analgesics for treatment of PDAC.

Drug class	Examples*	Comments
Non-opioid analgesics	paracetamol 1 g x 4	Used for milder pain. Due to gastrointestinal and cardiac side effects NSAIDs should normally be avoided. Metamizole may also be considered.
Weak opioids	tramadol CR 50–200 mg x 2	Codeine and tramadol potentiate the effect of non-opioid analgesics. Both are prodrugs, metabolized to active opioids and may result in the same side effects.
Strong opioids	oxycodone PR starting at 15 mg x 2	Addiction is not of major concern in PDAC associated with short life-expectancy, but escalation of dose can be problematic and some patients may develop opioid-induced hyperalgesia. Due to potential organ failure during progression of disease drugs without active metabolites are preferred.
Anticonvulsants	pregabalin titrated from 75 mg to 300 mg x 2 daily	The therapeutic gain is often limited due to the side effects (mainly drowsiness and dizziness), but often these vanish during treatment
TCA	amitriptyline 10–50 mg at nighttime	Side effects limit their use. The effects appear after several weeks of treatment. If one TCA does not work, another may be effective.
SSRI	citalopram titrated up to 40 mg at nighttime	This class is not an effective analgesic, but may be preferred by some patients in case of comorbid anxiety and depression
SNRI	duloxetine titrated up to 120 mg at nighttime	The effects of SNRI's are less well documented in cancer pain. They may be used when neuropathic pain is suspected, and for comorbid anxiety or depression
Anxiolytics	diazepam 5 mg x 3	Have limited, if any, analgesic effect, but may dampen anxiety
Anti-psychotics	levomepromazine titrated up to 100 mg daily	May potentiate the analgesic effect in selected patients as an augmentation strategy
α -adrenergic agents	clonidine titrated to 50 μ g x 2 daily	May potentiate analgesia when used as add on to the existing treatment, however side effects limit its use. Most evidence support parenteral and intrathecal use
NMDA inhibitors	ketamine titrated up to 50 mg x 3 daily	As the strongest NMDA inhibitor ketamine may be effective, but side effects are often severe (treated with concomitant administration of benzodiazepines).
Cannabinoids	nabilone dose 1–2 mg, up to 6 mg daily	Absorption following oral use is variable but can be used and is suggested here. Mostly used as adjunctive pain medication and useful for nausea, appetite and sleep. Small pain reduction and central nervous system side effects limit use in some patients, considered as third line agent
Steroids	dexamethasone 8 mg daily	The anti-inflammatory effects may be beneficial in selected cases
Anti-cholinergic drugs	hyoscine titrated to 20 mg x 4	Can be adjuvant therapy for bowel obstruction
GABA-agonists	baclofen titrated from 5 to 25 mg x 3	May be effective in neuropathic pain but is seldom used
Setrons	ondansetron 8 mg x 2	Normally used against nausea but may have an analgesic effect
Somatostatin analogues	octreotide depot 20 mg every 4th week	May be effective in bowel obstruction and potentially also has an analgesic effect. Oral use not possible, but injections with depot formulations may be used

NSAID: non-steroidal anti-inflammatory drugs.

TCA: tricyclic antidepressants.

SSRI: selective serotonin reuptake inhibitors.

SNRI: serotonin-noradrenalin reuptake inhibitors.

BZD: benzodiazepines.

GABA: gamma-aminobutyric acid.

* Examples are the authors own suggestions and reflect their normal practice. This varies between countries and regions and is dependent on traditions, availability of the drugs etc., and can only be regarded a suggestion for clinical management. For details see text.

proton pump inhibitor in case of patient preference. Metamizole is safer for the upper intestinal tract and kidneys than NSAIDs and is an alternative [20]. For more severe pain, combination therapies (also with opioids) may be necessary early in the disease. As shown in Fig. 1, *adjuvant analgesics* may be added. These are a heterogeneous group of drugs, which include antidepressants, anticonvulsants, and anxiolytics. In clinical practice, anti-neuropathic medications, such as gabapentin and amitriptyline, are often used. Most of the analgesics shown in Table 2 have not been systematically evaluated for pain associated with PDAC. However, pain mechanisms and symptoms are likely to be similar across different diseases [21]. In general, combination therapies are often more effective and may decrease the risk of side effects if lower doses can be used for individual drugs [22]. The choice of drugs is also determined by an assessment of patient co-morbidity, adverse effects and any desired side effects (such as sleep and anxiolytic action).

Anxiety and depression can be masked and screening with reliable and valid questionnaires can detect significant underlying emotional distress [23]. Such patients may benefit from drugs with combined analgesic and anti-depressive effects such as serotonin–norepinephrine reuptake inhibitors (SNRIs) that have less side effects than traditional tricyclic anti-depressives. Antidepressant drugs can also have neuromodulatory analgesic properties [24]. Psychotherapy should also be considered.

Opioid analgesics are the mainstay in the management of severe cancer pain. These are highly effective and their appropriate use by competent clinicians is important. Unfortunately, the drugs are often difficult to use and treatment may be complicated by severe adverse effects. The prescriber should therefore follow guideline recommendations [25–28]. Even with dose escalation, addiction is seldom a problem in patients with PDAC. Opioids should not be used alone, but added to a multidisciplinary strategy that includes all necessary adjuvant analgesics, psychological and social support. There is enormous variation in opioid availability around the world, and insufficient availability can lead to under-treatment [29,30]. In patients with progressive diseases like PDAC severe renal and hepatic insufficiency may develop over time and some opioids like codeine, tramadol and morphine require extra caution [25]. All patients must be fully informed of the proposed therapeutic strategy and potential side effects. In some cases, the abdominal pain increases despite an increase in opioid dose, and opioid induced bowel dysfunction (ileus and constipation) or opioid induced hyperalgesia (narcotic bowel syndrome) should be suspected [31,32]. Laxatives should be considered for all patients on opioid analgesia for PDAC pain because of the high risk of constipation. Other strategies include the use of opioid antagonists with restricted effect on the gut or in the periphery, or in case of hyperalgesia, opioid rotation or even lowering or tapering off opioids. Patients on opioid therapy must be kept under close clinical surveillance, and it should be noted that there is considerable individual variation in both efficacy and side-effects. Not all patients benefit from opioids and often additional treatments are required. A trial of an alternative opioid may also be indicated. *Opioid rotation* may be difficult and patients with pain may need higher doses than patients who are switched because of intolerable side effects [13,29]. Transdermal administration (patch formulation) may be useful in patients having trouble with oral intake. Breakthrough pain can be treated with rapid-onset transmucosal or intranasal fentanyl formulations. Methadone may be advantageous in many patients and can be used in small doses as add-on to existing opioid treatment. Of note, methadone should only be prescribed by physicians who are familiar with the complex pharmacology and adverse effect profile of this opioid.

In case of poor pain control, continuous pharmacotherapy by

means of epidural or intrathecal catheters might be considered. When pain is caused by liver or bone metastases, patients may benefit from radiotherapy [12].

Supplementary treatments such as cannabinoids, ketamine, clonidine, benzodiazepines, anti-psychotics and steroids may be considered in difficult cases [13]. For management of pain in PDAC, cannabinoid derivatives are mostly prescribed in the palliative phase. Nausea, low appetite and poor sleep are additional targets. Although small series report modest pain relief with dronabinol in gastro-intestinal cancers, sound clinical evidence is lacking [33–35]. Evidence is scarce for ketamine in cancer pain. The drug may reduce opioid-induced tolerance and hyperalgesia which is beneficial for many patients. The mode of administration is still not standardized with some support for intravenous or subcutaneous use [36] or intranasal administration [27].

Near the *end-of life*, pain management for advanced and terminal PDAC can become very challenging and an interdisciplinary approach, including palliative care specialists is needed. It is important wherever possible to consider the preferences of the patient. Depending on the national legal and ethical framework, a range of supportive care measures can be offered, including intensive home support, home care with parenteral opioids, patient controlled analgesia and palliative sedation. Finally, in some countries, patients with terminal cancer have the legal right to request euthanasia or assisted suicide [37].

Invasive management of PDAC

Neurolytic treatment

Neurolysis in PDAC can reduce pain intensity and opioid use, but as the duration of effect is highly variable it is normally reserved for palliating patients with advanced stages of disease and short life expectancy. Celiac plexus neurolysis is most used and bilateral injection or direct injection in the ganglia is recommended. The endoscopic approach may decrease the risk of complications. Other procedures such as splanchnicectomy are less well documented and seldom used, although it may relieve pain for a longer time period. Quality assessment: moderate; Recommendation: strong; Agreement: strong

Neurolytic procedures of the sympathetic nervous system have been used for nearly a century to treat pain in patients with PDAC [38]. The rationale is to reduce pain by destruction of the afferent pathways from pancreas to the brain, and can be done at different levels (Fig. 2); for more details please see appendix. One of the most commonly used procedures is celiac plexus neurolysis (CPN). Importantly, only the upper abdominal visceral pain sensations are targeted.

Celiac plexus neurolysis

Technique: The classic technique is the bilateral, percutaneous posterior approach, guided fluoroscopically or with computed tomography. When the needle is in the correct position a neurolytic agent, typically absolute alcohol, is injected around the nerves [39]. In cases of advanced cancers, the analgesic effect of CPN may be limited [40], and malignant infiltration of the plexus is also a predictor of poor pain response [41]. While a few studies found no differences between central versus bilateral injections [42,43], a randomized study and a meta-analysis have shown superiority of bilateral injections [44,45].

Efficacy: There is evidence that CPN, regardless of the technique used, improves analgesia and QoL, and decreases opioid consumption [26,46]. Compared with analgesic drugs, there is minimal superiority, but CPN is associated with fewer adverse effects [46,47]. Unfortunately, most studies have focused on pain intensity rather than more composite endpoints [48], and only a few are

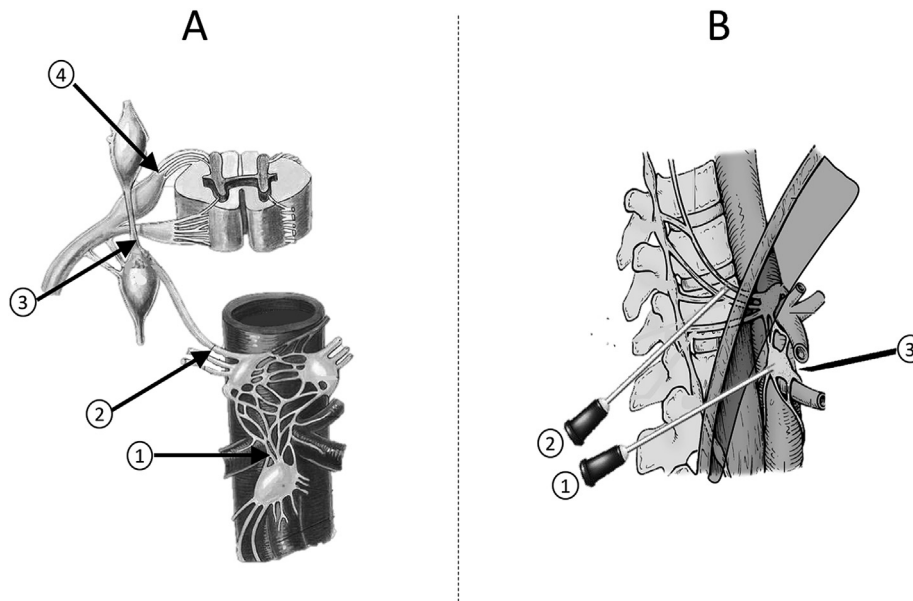


Fig. 2. Different approaches to neurolytic therapy in PDAC. A: Potential levels of neurolysis. 1) Celiac plexus block; 2) Splanchnicectomy; 3) Sympathectomy; 4) Rhizotomy. The two latter are seldom used. B: Schematic illustration of the most used procedures. 1) Percutaneous transcrural celiac plexus neurolysis; 2) Percutaneous retrocrural splanchnic nerve neurolysis (the thoracoscopic splanchnicectomy is not shown); 3) Endoscopic ultrasonography-guided celiac plexus neurolysis (bilateral, broad or intraganglionic neurolysis is the recommended technique).

considered of high quality [39,46,49]. Importantly, if malignancy involves areas of somatic innervation such as the peritoneum or diaphragm, neurolysis will lose its effect.

Timing: Due to the risk of fibrosis and other complications, CPN is normally not performed before surgery. Some studies proposed early intervention [50–53]. However, these observations remain unproven since CPN was often performed in patients receiving analgesic drugs [54]. The analgesic effect seems to vanish after 8 weeks [49], and in most patients, pain recurs after 3 months [50]. As only about 30% of patients benefit from repeated CPN [55], this is normally not offered. As the probability of patients remaining completely pain free after CPN diminishes with increasing survival time, the optimal therapeutic window may be in later stages of disease so the effect is maximal when pain intensity is highest [53,54]. The arguments against late intervention is that tumor growth may involve other organs, where CPN is less effective. There is significant variation in the analgesia duration, and timing will differ between patients. Overall there is general agreement that neurolysis is best reserved for patients with advanced disease, and indicated when strong analgesics are no longer effective or their side effects increase QoL [56]. Life expectancy, and extent and rate of disease progression should be considered in individual patients.

Survival: Weak clinical evidence indicates that opioids (as the alternative to neurolysis) may play a negative role in cancer development and progression [57,58]. CPN could at least theoretically be opioid sparing and prolong survival. Additionally, PDAC has neurotrophic characteristics and as tumor growth may follow the nerves, destruction of the pathways could be advantageous [59]. Correspondingly, an early study showed prolongation of survival after performing CPN [50], but this was not reproduced in later retrospective studies [60] and there is no robust evidence that CPN affects progression of disease.

Endoscopic ultrasonography-guided celiac plexus neurolysis (EUS-CPN): This is becoming increasingly popular as it has fewer risks. Due to the variation of the anatomy of the celiac trunk, EUS also has the advantage of allowing direct visualization of the celiac ganglia [61]. The use of Doppler makes it possible to assess the

regional vascular structures and reduce the risk of posterior spread of the neurolytic agent to the spinal arteries or nerves. Another advantage is that the procedure can be performed at the same time as fine needle aspiration for cytology in patients with unresectable and metastatic PDAC [39,41,62]. Contraindications to EUS-CPN include uncorrectable coagulopathy, esophageal or cardiac varices, altered anatomy of the upper digestive tract secondary to previous surgery, hemodynamic/respiratory instability, large tumor mass and lymphadenopathy [62].

No large trials have directly compared EUS-CPN with the classical percutaneous approach, but relief of pain was reported in 54%–88% of cases in several case series together with a decrease in opioid consumption [41,63–65]. In most case series, the duration of pain relief in the successful treatment group was reported around a median of 8–10 weeks and until death in one third of patients [41,62,66]. Like for the percutaneous approach, bilateral injection of the celiac plexus seems to provide better pain relief than injecting at one site [44,65]. Broad neurolysis and direct injection into the celiac ganglia may also be better than unilateral injections [67,68].

Splanchnic nerve neurolysis

Splanchnicectomy may disrupt more nerve pathways than CPN (Fig. 2) and is a better alternative when there is a large mass in the region of the celiac plexus. The procedure is most often performed thoracoscopically under general anesthesia, but can also be performed fluoroscopically as a day care procedure. Splanchnicectomy is seldom performed in patients with PDAC despite some evidence of long lasting pain relief and few complications in observational series [69–72], possibly because the expertise is not widely available. Splanchnicectomy with radiofrequency ablation seems less effective, but reports are limited. A retrospective study showed a long-lasting effect on pain with no severe complications [73], but randomized trials are lacking.

Other neurolytic techniques

Combined tumor ablation and celiac plexus neurolysis with EUS was recently shown to be more effective for pain relief and survival

than EUS guided neurolysis alone, and this may be an approach for future treatment [74]. Other endoscopic techniques include celiac ganglion irradiation with I-125 impregnated seeds [75,76]. In pilot studies, this has been shown successful in the short run and a recent meta-analysis confirmed an effect on pain in 80% of patients [77].

Complications of neurolysis

Although CPN is generally safe, common side effects include transient orthostatic hypotension, diarrhea and back pain. Neurological complications related to spasm or thrombosis of the anterior spinal artery are seldom (<0.15%) seen, but cases of paraplegia have also been reported [78]. Retroperitoneal hemorrhage and infections may also develop, and peripancreatic and brain abscesses have been described [79,80] (see Table 3).

Neuromodulation

Acupuncture is a moderately effective treatment for cancer pain, including PDAC. The evidence for an analgesic effect from transcutaneous electrical nerve stimulation is weak. The procedures can be considered as supplementary treatments in selected patients. Quality assessment: low; Recommendation: weak; Agreement: conditional

Acupuncture has been widely used for cancer pain in China, and appears to be moderately effective in selected patients [56,81]. An analgesic effect was found using electro-acupuncture compared with sham in patients with PDAC, and this effect persisted for up to two days after cessation of treatment [82]. Acupuncture has few if any side-effects, but is operator dependent and the effect is normally short-lasting. Therefore, it can be regarded as a supplementary treatment to other therapies.

The evidence for an analgesic effect with transcutaneous electrical nerve stimulation (TENS) is weak, but may be helpful in selected patients [83]. Spinal cord stimulation is rarely used because it is a more invasive and costly procedure for patients that have a limited life expectancy. Another approach to neuromodulation is vagal stimulation, which might be effective in selected patients [84].

Radiotherapy and ultrasound

Radiotherapy appears to be effective for PDAC pain, but prospective

evidence is required before it can be generally recommended. Quality assessment: low; Recommendation: weak; Agreement: conditional

The effect of radiotherapy on pain has been studied both in patients with chronic pancreatitis [85] and PDAC [86,87], but the evidence comes from observational studies. It may be suitable for frail patients and requires further evaluation [88]. A pilot study showed that stereotactic radiotherapy (CyberKnife) could alleviate pain in patients with metastatic PDAC and may be useful in selected cases [89].

Pilot data from observational series suggest that high intensity focused ultrasound (HIFU) improves pain and physical function [90,91], and this was confirmed in a recent meta-analysis [92]. Despite this, the heterogeneity of the data and the lack of randomized controlled trials prevents making a strong recommendation.

Endoscopic treatment

Pancreatic ductal stenting can be considered for a small subgroup of patients with unresectable PDAC in the head of pancreas, dilation of the main pancreatic duct and severe “obstructive-type” pancreatic pain. Quality assessment: low; Recommendation: moderate; Agreement: conditional

Several case series have reported that pancreatic ductal stenting can help to palliate pain [93]. It appears that this is indicated in a small subgroup of patients with unresectable PDAC in the head of pancreas, associated with dilation of the main pancreatic duct (MPD) and with severe pancreatic obstructive-type of pain (see supplementary material). Pain relief was reported in about 80% of these cases [93]. A prospective study reported a decrease in pain intensity and reduced opioid consumption over 16 weeks in 62% of patients [94]. In another prospective study, it was found that pain relief was only found in patients with a dilated MPD [95]. Pancreatic ductal stenting could therefore be considered in those patients with unresectable pancreatic cancer in the head of pancreas, severe “obstructive-type” pancreatic pain, and MPD dilatation. While this could be considered at the same time as biliary stenting, there is a lack of randomized controlled studies comparing it with other pain treatment and it cannot be recommended as a standard of care [96].

Table 3

Frequently asked question about neurolytic therapy.

Clinical question	Recommendation
Is CPN better than standard therapy?	RCTs have shown that CPN decrease pain and opioid consumption in comparison with conventional therapy, but the difference in effect is marginal
When shall CPN be done?	The timing cannot be predicted by any clinical parameters. Most studies recommend that analgesics are used first and neurolysis done when pain cannot be controlled or opioid consumption is accelerated. As efficacy decrease after 2–3 months it shall be postponed to the later stages of disease and life expectancy taken into consideration
Can CPN be repeated?	Technically it can, but is only effective in about 30%, partly because tumor growth may extend to other tissue
Which technique shall be used?	The EUS approach is considered safer although evidence is limited, but when available it is recommended. In centers with major experience in imaging guided percutaneous CPN this may be preferred.
What does tumor localization mean?	Localized disease may respond best. Although some studies have shown better effect in certain locations (head, body tail) there is no consensus
Does CPN prolong survival?	Although there may be a theoretical gain, clinical studies do not support an effect on disease progression
Are other techniques for CPN advantageous?	There is no solid evidence that other neurolytic techniques are better, but pilot studies seem to indicate that for example broad neurolysis and combined CPN and tumor ablation gives better response than standard treatment
Has splanchnicectomy any advantages compared to CPN?	Potentially splanchnicectomy is better when a large mass is present around the celiac plexus and disrupt more nerve pathways than CPN. However, comparative studies are lacking.
Are there any predictors for effect?	Tumor location does not seem to interfere with pain relief, but involvement of the celiac plexus may complicate the procedure. Involvement of structures outside pancreas may also decrease analgesia as neurolysis only blocks the sympathetic pathways of visceral pain
Are there any technical considerations?	The effect seems to be better when the neurolytic agent has a broad distribution, and when the celiac ganglia are directly visualized endoscopically and injected

CNP: celiac plexus neurolysis and RCT: randomized controlled trial

Surgical treatment

The role of surgical treatment to palliate pain associated with PDAC is extremely limited, although surgery may be rarely indicated for pain due to duodenal or biliary obstruction. Quality assessment: moderate; Recommendation: strong; Agreement: strong

Historically, surgical treatments were used for the division of putative pain pathways, including celiac plexi, splanchnic nerves, sympathetic chain and spinal nerve roots (see Fig. 2). These surgical neurolytic procedures have fallen into abeyance with the failure of evidence for a favorable risk:benefit ratio and with the rise of minimally invasive alternatives [97]. Pain relief is expected when complete surgical resection of PDAC is possible, as a surgery first approach or after neoadjuvant therapy. However, pain is most commonly associated with locally advanced PDAC (either primary or as recurrence), where there is direct tumor extension beyond the pancreas, along with perineural and lymphovascular invasion. Because of the morbidity (including pain), risk of mortality and delayed recovery, *palliative pancreatic resections* are no longer recommended [98]. This is reflected in the significantly reduced need for surgery as a palliative intervention, and the increasing use of palliative chemotherapy for stage IV PDAC [99].

Pain can also be due the invasion of adjacent organs by PDAC, and surgery may play a role in these circumstances. *Stenosis of the distal bile duct* can in some cases give rise to biliary type pain with obstructive jaundice, but endoscopic biliary stenting is now used in the vast majority of patients [100]. Stenting of the bile duct rarely gives rise to painful *acute cholecystitis* [101], and if antibiotics and endoscopic treatments are not effective, a percutaneous trans-hepatic cholecystostomy or cholecystectomy may be required. Stenting can also be associated with ascending cholangitis and pain and this necessitates stent exchange. Advanced PDAC can also cause pain associated with *gastric outlet obstruction* secondary to duodenal invasion and stenosis. Historically, surgical treatment was used, but endoscopic duodenal stenting is now preferred [100].

Psychosocial interventions

There is moderate evidence in favor of psychosocial interventions for cancer pain in general, but the evidence is limited for PDAC. Pooled data suggest moderate efficacy with pain relief. Quality assessment: moderate; Recommendation: moderate; Agreement: strong

Anxiety and depressive symptoms are common in PDAC, with rates higher than for other cancers in most studies [102–106]. In one study, the severity of depression was linked to increased self-reported pain [105]. Depression has been linked to significantly poorer QoL [107]; sleep disturbance [108], inadequate cancer treatment and lower survival rates [109]. Because depression, anxiety, pain, sleep disturbance and negative or pessimistic thoughts or attitudes are modifiable conditions, proper assessment and management is essential [110].

There has been no randomized control trial of any behavioral intervention for patients with PDAC, but an open pilot study showed a beneficial effect of educational sessions by nurses on QoL [111]. One opinion article recommended a psycho-oncologist for PDAC patients to distinguish normal emotional reactions to cancer which usually resolve within weeks, with appropriate social support from longer lasting psychiatric conditions requiring psychotherapy and psychotropic medications [112].

Suggested psychosocial approaches can be drawn from studies for other types of cancers with a similar psychological symptom profile. Supportive therapy, cognitive behavioral therapy, coping skills training, mindfulness meditation, hypnosis, dignity therapy and acceptance and commitment therapy have the strongest evidence of efficacy [113–120]. Overall, most studies support the idea

that psychosocial interventions offered early in the cancer course have a more significant benefit than those offered at end-stage disease [121,122].

Supportive and palliative care

The provision of palliative care to patients with newly diagnosed and incurable PDAC improves quality of life, reduces depression, and an analgesic effect is expected. Quality assessment: low; Recommendation: moderate; Agreement: strong

The goal of palliative care, in taking a holistic approach to care and treatment, is to improve the QoL of patients with advanced cancer by alleviating symptoms and problems caused by illness and its treatment [123]. The early provision of palliative and oncology care in patients with newly diagnosed incurable cancers (including PDAC) improves QoL, reduces depression symptoms, and enhances the ability to cope with the diagnosis and prognosis [124,125]. As a result, an analgesic effect is expected. A recent retrospective study showed that patients with advanced PDAC benefited from a palliative care programs by requiring less chemotherapy and less admission to intensive care and hospital [126]. Palliative care of patients with PDAC should include nutritional support and optimized pancreatic enzyme replacement [12].

Systematic early palliative care was shown to be superior to on-demand palliative care in terms of QoL (and probably pain relief) [127]. The actual evidence for the efficacy of early palliative care interventions is still sparse, but it generally accepted that this should be recommended for all patients with advanced PDAC.

Conclusion

Unfortunately, most patients with pancreatic ductal adenocarcinoma have unresectable disease and succumb to local recurrence and metastatic disease. Therefore, they often need advanced therapy as part of palliative care. The overall management requires the coordination of multiple disciplines and this is particularly true for associated pain, which can be disabling and arises due to a number of different mechanisms. The assessment of pain must take into account other symptoms and the broader context of other physical and psychological symptoms. The many treatment options have been reviewed and an international, multidisciplinary consensus obtained, including the strength of recommendation and the extent of agreement. An algorithm is presented which brings together all treatment options, but there are few comparative studies to help define which combination and order of these treatment options should be applied to the management of individual patients. This might go some way to explaining the variation of practice and opinion, amongst international experts. Management of pain should always be multimodal and individualized, and will depend on factors such as disease stage, patient preferences and local expertise. However, it is strongly recommended that all possible treatment options are considered, preferably in a multidisciplinary setting, to ensure optimal care.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.pan.2018.04.008>.

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